REMARKS

The Examiner has acknowledged Applicants' election with traverse to pursue nucleic acid claims 1-21 (Group I) for prosecution in this application. The Examiner has rejoined protein claims 22 and 23 (Group II). Additionally, the Examiner has withdrawn the species election requirement. As such, claims 1-23 have been examined on the merits. Claims 24-29 have been withdrawn from consideration as being drawn to non-elected subject matter.

Applicants also note that the Examiner considers the claims free of the prior art.

Claims 12-15 have been canceled without prejudice or disclaimer. Claims 6-9, 11, 22 and 23 have been amended. New claim 30 has been added. Support for claim 30 and the amendments my be found throughout the specification but particularly in Table 1. No new matter has been added.

Applicants respectfully assert that the amendments bring the claims into condition for allowance.

1. Formal Matters

The Applicants have amended the drawings and the specification in accordance with the Examiner's concerns in the stated objections. Applicants also delete Figures 7-9 per the Examiner's suggestion.

Applicants submit that the amendments fully address the objections and withdrawal thereof is requested.

2. Rejections under 35 U.S.C. §112

2.1 Rejection under 35 U.S.C. §112, second paragraph

The Examiner rejects claims 1-23 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicants respectfully disagree.

2.1.1 "Stringent conditions"

It is argued that the claim recitation "stringent conditions" is indefinite because the specification's description of stringent conditions is non-limiting and therefore vague and indefinite.

"The essential inquiry" under 35 U.S.C. 112, second paragraph, "is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity." MPEP 2713.02. As explained below, the claims at issue readily comply.

Acting as their own lexicographers, Applicants have defined 'stringent conditions' in the Application. MPEP 2173.01 (A "fundamental principle contained in 35 U.S.C. 112, second paragraph is that applicants are their own lexicographers."). The MPEP provides that the claims "must be analyzed" in light of the lexicography in the Application's disclosure. *Id.* Reviewing the claims at issue, one of ordinary skill in the art would be apprised of the scope of the claims, being clearly warned as to what would constitute infringement. MPEP 2173.02 (*citing Solomon v. Kimberly Clark Corp.*, 216 F.3d 1372, 1379 (Fed. Cir. 2000). The MPEP teaches that the Examiner should give "[s]ome latitude in the manner of expression and the aptness of terms" so long as the Applicants have satisfied the statutory requirements. MPEP 2173.02. All that is needed is for the Applicants to describe the patentable subject matter with "a reasonable degree of particularity and distinctness" to one of ordinary skill in the art. *Id.* (emphasis in original).

The term "stringent conditions" is well known in the art, and would not be indefinite even if undefined in the specification. MPEP 2173.02 (Even if a claim term is not defined in the specification it is not indefinite if the meaning of the claim term is discernable to one of ordinary skill in the art) (citing *Bancorp Services, L.L.C. v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1372 (Fed. Cir. 2004). Nevertheless, over the course of three paragraphs on pages 22 and 23, the specification defines "stringent conditions" with reasonable clarity such that it would be understood by one of ordinary skill in the art.

To briefly summarize the three paragraphs, the first paragraph sets forth basic criteria by which one of ordinary skill could evaluate whether stringent conditions exist in a sample. Page 22, line 24 to page 23, line 3. The second paragraph explains how one of ordinary skill would use temperature to generate the appropriate stringent conditions specific for the buffer being used. Page 23, ll. 4-15. The third paragraph provides an illustrative example of the appropriate stringent conditions when using the buffer SSC, and also incorporates by reference the methods for generating stringent conditions set forth in two standard molecular biology handbooks, methods consistent with the specification and which one of ordinary skill in the art would have familiarity with. Page 23, ll.16-24.

Examining these paragraphs more closely, the first paragraph sets forth two, generally understood guidelines by which one of ordinary skill in the art would determine whether stringent conditions exist. The paragraph first sets forth that such conditions "preferably" "prevent hybridization of nucleic acids having 3 or more mismatches out of 20 contiguous nucleotides, more preferably 2 or more mismatches out of 20 contiguous nucleotides, most preferably one or more mismatch out of 20 contiguous nucleotides." Page 22, line 28 to page 23, line 1. Stated slightly differently, under stringent conditions, the "hybridizing portion of the hybridizing nucleic acid is at least about 90%, preferably at least about 95%, or most preferably about at least 98%, identical to the sequence of a target sequence, or its complement." Page 23, ll. 1-3.

In the second paragraph, the specification explains how one of ordinary skill in the art would create the appropriate stringent conditions, *e.g.*, by adjusting for the salt concentration and modulating the temperature of the buffers being used. In other words, the Application does not limit stringent conditions to a single buffer, but teaches the generally understood technique that temperature is modified to set the stringent conditions depending on the salt concentration in the buffers being used for hybridization and washing. Page 23, ll.16-24.

The specification then goes on to describe how stringent conditions are used to isolate sequences that are *substantially identical* to a predicate sequence (rather than identical). The Application explains it is useful to first establish the lowest temperature at which only *homologous hybridization* occurs with a particular concentration of salt (*e.g.* SSC). p. 23, ll. 10-12. The Application then explains that assuming that 1% mismatching results in a 1^{O} C decrease in T_m, the temperature of the final wash in the hybridization reaction is reduced accordingly (for example, if sequences having >95% identity with the predicate sequence are sought, the final wash temperature is decreased by 5^{O} C), and that in practice, the change in T_m can be between 0.5^{O} C. and 1.5^{O} C. per 1% mismatch. Page 23, ll. 11-16.

In the third paragraph, the specification provides an illustrative example of what the stringent conditions would be when using SSC as a buffer. As described, the stringent conditions for a hybridization using the buffer SSC would be hybridization at 68^{O}C. in 5xSSC/5x Denhart's solution/1.0% SDS, and washing in 0.2xSSC/0.1% SDS. Page 23, ll. 16-17. This third paragraph also incorporates two basic molecular biology texts, Molecular Cloning and Current Protocols in Molecular Biology. p.23, ll. 20-24. Both of these texts describe the

common methods used by one having ordinary skill in the art to discern the stringent conditions specific for the buffer being used.

Given this disclosure and the basic knowledge of the skilled artisan, Applicants respectfully submit that they have set forth with reasonable clarity how one of skill in the art could readily determine appropriate salt concentrations and temperatures for hybridization and washing to facilitate the hybridization of two nucleic acid sequences wherein there is at least about 90%, preferably at least about 95%, or most preferably about at least 98%, identity between their hybridizing portions.

2.1.2 Claim 7

The Examiner rejects this claim for allegedly not reciting a claim to a particular subject matter. Applicants have made the appropriate correction to claim 7.

2.1.3 Claims 6, 8, 9, 11-15

The Examiner argues that each pair of claims 6 and 12; 8 and 13; 9 and 14; 11 and 15; relate to the same respective protein. The Examiner asserts that there is no difference in scope between the functional limitations, "which upon binding an epoxy farnesoid-like ligand results in transcriptional activation of a nuclear hormone receptor reporter construct," and "which has dominant negative nuclear hormone receptor activity." Moreover, the Examiner argues that the former limitation is indefinite because it is not clear how the claimed mutant proteins can transcriptionally activate a nuclear hormone receptor reporter construct and have dominant negative nuclear hormone receptor activity at the same time. Applicants respectfully disagree.

However, in order to facilitate prosecution of the Application, Applicants have amended claims 6-9 and 11 to recite nucleic acids encoding proteins that have altered fluorescent properties with respect to wild type USP upon ligand binding. Applicants have also canceled claims 12-15 without prejudice or disclaimer.

2.1.4 Claims 22 and 23

The Examiner rejects claims 22 and 23 as indefinite for improper multiple dependency claim language. Applicants have amended these claims to address the Examiner's concerns.

Applicant asserts that the amendments and remarks fully address these rejections and respectfully request their withdrawal.

2.2 Rejection under 35 U.S.C. §112, first paragraph

The Examiner rejects claims 6, 8, 9 and 11-15 under 35 U.S.C. §112, first paragraph, for allegedly not being enabled. The claims at issue define the USP mutants in terms of their ability to induce transcriptional activity and have dominant negative activity. The Examiner argues that it would take undue experimentation to determine how this could be possible give that "weak" dominant negative activity is not explicitly defined. Applicants respectfully disagree.

However, in order to facilitate prosecution of the Application, Applicants have amended claims 6-9 and 11 to recite nucleic acids encoding proteins that have altered fluorescent properties with respect to wild type USP upon ligand binding. Applicants have also canceled claims 12-15 without prejudice or disclaimer.

Applicant asserts that the amendments and remarks fully address this rejection and respectfully request its withdrawal.

CONCLUSION

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

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